Predictors of poor response to methotrexate in polyarticular-course juvenile idiopathic arthritis: analysis of the PRINTO methotrexate trial

Vilca, I ; Munitis, P G ; Hofer, M

Abstract: OBJECTIVES: To determine whether baseline demographic, clinical, articular and laboratory variables predict methotrexate (MTX) poor response in polyarticular-course juvenile idiopathic arthritis. METHODS: Patients newly treated for 6 months with MTX enrolled in the Paediatric Rheumatology International Trials Organization (PRINTO) MTX trial. Bivariate and logistic regression analyses were used to identify baseline predictors of poor response according to the American College of Rheumatology pediatric (ACR-ped) 30 and 70 criteria. RESULTS: In all, 405/563 (71.9%) of patients were women; median age at onset and disease duration were 4.3 and 1.4 years, respectively, with anti-nuclear antibody (ANA) detected in 259/537 (48.2%) patients. With multivariate logistic regression analysis, the most important determinants of ACR-ped 70 non-responders were: disease duration > 1.3 years (OR 1.93), ANA negativity (OR 1.77), Childhood Health Assessment Questionnaire (CHAQ) disability index > 1.125 (OR 1.65) and the presence of right and left wrist activity (OR 1.55). Predictors of ACR-ped 30 non-responders were: ANA negativity (OR 1.92), CHAQ disability index > 1.14 (OR 2.18) and a parent's evaluation of child's overall well-being < or = 4.69 (OR 2.2). CONCLUSION: The subgroup of patients with longer disease duration, ANA negativity, higher disability and presence of wrist activity were significantly associated with a poorer response to a 6-month MTX course.

DOI: https://doi.org/10.1136/ard.2009.120840

ARD Online First, published on June 4, 2010 as 10.1136/ard.2009.120840

Predictors of poor response to methotrexate in polyarticular-course juvenile idiopathic arthritis: analysis of the PRINTO methotrexate trial

Iris Vilca,[1] Pablo Garcia Munitis,[1] Angela Pistorio,[2] Angelo Ravelli,[3] Antonella Buoncompagni,[1] Blanca Bica,[4] Lucia Campos,[5] Renate Häfner,[6] Michael Hofer,[7] Seza Ozen,[8] Christian Huemer,[9] Sang Cheol Bae,[10] Flavio Sztajnbok,[11] Olga Arguedas,[1] Ivan Foeldvari,[12] Hans Iko Huppertz,[13] Maria Luz Gamir,[14] Bo Magnusson,[15] Frank Dressler,[16] Yosef Uziel,[17] Marion A J van Rossum,[18] Peter Hollingworth,[19] Gail Cawkwell,[20] Alberto Martini,[3] Nicolino Ruperto[1]; for the Pediatric Rheumatology International Trials Organisation (PRINTO)

For numbered affiliations see end of article

Correspondence to
Nicolino Ruperto, IRCCS G Gaslini, Università di Genova, Pediatria II – Reumatologia, Largo Gaslini, 5, 16147 Genova, Italy; nicolaruperto@ospedale-gaslini.ge.it

Accepted 26 January 2010
IV and PGM contributed equally to this work.

ABSTRACT

Objectives To determine whether baseline demographic, clinical, articular and laboratory variables predict methotrexate (MTX) poor response in polyarticular-course juvenile idiopathic arthritis.

Methods Patients newly treated for 6 months with MTX enrolled in the Paediatric Rheumatology International Trials Organization (PRINTO) MTX trial. Bivariate and logistic regression analyses were used to identify baseline predictors of poor response according to the American College of Rheumatology pediatric (ACR-ped) 30 and 70 criteria.

Results In all, 405/563 (71.9%) of patients were women; median age at onset and disease duration were 4.3 and 1.4 years, respectively, with anti-nuclear antibody (ANA) detected in 259/537 (48.2%) patients. With multivariate logistic regression analysis, the most important determinants of ACR-ped 70 non-responders were: disease duration >1.3 years (OR 1.93), ANA negativity (OR 1.77), Childhood Health Assessment Questionnaire (CHAQ) disability index>1.125 (OR 1.65) and the presence of right and left wrist activity (OR 1.55). Predictors of ACR-ped 30 non-responders were: ANA negativity (OR 1.92), CHAQ disability index>1.14 (OR 2.18) and a parent's evaluation of child's overall well-being ≤4.69 (OR 2.2).

Conclusion The subgroup of patients with longer disease duration, ANA negativity, higher disability and presence of wrist activity were significantly associated with a poorer response to a 6-month MTX course.

INTRODUCTION

Methotrexate (MTX) up to 15 mg/m^2/week for 9–12 months is the second line agent of first choice for the treatment of children with polyarticular-course juvenile idiopathic arthritis (JIA) who do not respond to non-steroidal anti-inflammatory drugs.[1–3] About one-third of these patients do not respond or are intolerant to MTX and are, therefore, candidates for treatment with biological agents.[4–7]

Knowledge of predictive factors of poor drug response is of great value in clinical practice[8–10] to identify patients who are likely to have progressive disease and may need aggressive treatment earlier.

The purpose of the present study, conducted by the Paediatric Rheumatology International Trials Organization (PRINTO)[11] was to determine, in a post hoc trial analysis, whether baseline demographic, clinical, articular and laboratory variables can be used to predict poor response to treatment with MTX.

METHODS

Patient selection

Patients were extracted from the PRINTO database containing the results of a randomised trial aimed to evaluate the efficacy and safety profile of MTX in polyarticular-course patients with JIA[12 13] (rheumatoid factor (RF) negative, psoriatic arthritis and enthesitis-related arthritis excluded) as previously described.[2] A total of 563/595 (94.6%) patients with baseline and 6 months follow-up were included.

Evaluation of response to treatment

After 6 months of MTX treatment, patients were divided into responders and non-responders, according to the American College of Rheumatology pediatric (ACR-ped) 30 or 70 improvement criteria[14]: at least 30 or 70% (ACR-ped 30 or 70) improvement from baseline in at least three of any six JIA core set variables (doctor's and parent's evaluation, number of active joints and joint with limited range of motion, Childhood Health Assessment Questionnaire (CHAQ), erythrocyte sedimentation rate (ESR)) with no more than one of the remaining variables worsened by more than 30%.

Potential baseline predictors of response included demographic (gender, age at onset, at visit and disease duration), clinical (JIA subtype, uveitis, core set parameters), articular (76 individual or combined group of joints) and laboratory variables (anti-nuclear antibody (ANA) positivity according to International League of Associations for Rheumatology (ILAR) criteria, and ESR), as derived from the literature,[1 3 9 15–30] and as detailed in tables 1 and 2.

Statistics

Descriptive statistics were reported in terms of medians with first and third quartiles for quantitative variables and in terms of absolute frequencies and percentages for qualitative variables.

In the bivariate analysis the comparison of quantitative variables between two groups of patients

Table 1 Demographic and clinical characteristics of the study patients at baseline; patients are divided into responders and non-responders based on the American College of Rheumatology pediatric (ACR-ped) 30 and 70 dichotomous level of response

Characteristics	ACR-ped 30 responders (430 (76.4%))	ACR-ped 30 non-responders (133 (23.6%))	ACR-ped 70 responders (225 (40%))	ACR-ped 70 non-responders (338 (60%))
Demographics, N (%)				
Female	309 (71.9%)	96 (72.2%)	162 (72.0%)	243 (71.9%)
Age group				
≤ 4 years	104 (24.2%)	25 (18.8%)	58 (25.8%)	71 (21.0%)
>4 and ≤ 8 years	116 (27.0%)	44 (33.0%)	66 (29.3%)	94 (27.8%)
>8 and ≤ 12 years	129 (30.0%)	32 (24.1%)	58 (25.8%)	103 (30.5%)
>12 years	81 (18.8%)	32 (24.1%)	43 (19.1%)	70 (20.7%)
JIA subtypes				
Polyarthritis RF negative	243 (56.5%)	63 (47.4%)	123 (54.7%)	183 (54.1%)
Extended oligoarthritis	132 (30.7%)	44 (33.1%)	71 (31.5%)	105 (31.1%)
Systemic onset arthritis with polyarticular course	55 (12.8%)	26 (19.5%)	31 (13.8%)	50 (14.8%)
ANA				
Positive	214/409 (52.3%)***	45/128 (35.2%)	122/209 (58.4%)***	137/328 (41.8%)
Negative	195/409 (47.7%)	83/128 (64.8%)	87/209 (41.6%)	191/328 (58.2%)
NSAIDs	350 (81.4%)	108 (81.2%)	177 (78.7%)	281 (83.1%)
Steroids	108 (25.1%)	44 (33.1%)	61 (27.1%)	91 (26.9%)
MTX oral	330/428 (77.1%)	107 (80.5%)	168/224 (75%)	269/337 (79.8%)
MTX dose, mg/m^2/week (N=557)	10 (9.1–11.1)	10 (8.9–11.4)	10 (9.1–11.1)	10 (9–11.4)
Age at onset, years	4.4 (1.9–8.4)	4.2 (2.2–8.4)	4.4 (1.9–8.5)	4.3 (2.1–8.3)
Age at visit, years	7.8 (4.3–11.2)	7.5 (4.7–11.8)	7.3 (3.7–11.3)	8.1 (4.6–11.5)
Disease duration, years	1.3 (0.6–3.5)	1.7 (0.8–3.7)	1 (0.6–2.4)***	1.7 (0.8–3.7)
ESR (N=556)	40 (22–63)	37.5 (20–57.5)	44 (26–65)**	36 (20–59)
Doctor evaluation of physical well-being (N=559)	5.2 (3.7–6.6)	4.9 (3.7–7.0)	5.2 (3.8–6.6)	5.0 (3.6–6.6)
Parent's evaluation of child's overall well-being	4.6 (2.3–6.4)*	3.7 (2.0–6.1)	4.6 (2.2–6.2)	4.2 (2.2–6.3)
Parent's evaluation of child's pain (N=560)	4.7 (2.5–7.0)	4.4 (2.4–6.3)	4.5 (2.4–7.1)	4.5 (2.4–6.8)
CHAQ disability index	1.12 (0.62–1.75)	1.37 (0.62–1.87)	1 (0.62–1.62)*	1.37 (0.62–1.87)
CHQ PhS (N=438)	40.4 (29.6–46.9)	40.9 (32.4–46.5)	40.4 (29.7–47.9)	40.5 (30.8–46.4)
CHQ PsS (N=438)	46.1 (37.9–51.1)	46.8 (39.7–52.6)	46.1 (37.7–51.3)	46.4 (38.3–51.5)

Data are N (%) or median (first to third quartile). The denominator is indicated in the table header unless otherwise stated (eg, ANA or CHQ). Comparisons of frequencies was by χ^2 test, comparison of quantitative variables was by Mann–Whitney U test.
*p<0.05; **p<0.01; ***p<0.001.
ANA, anti-nuclear antibody; CHAQ, Childhood Health Assessment Questionnaire; CHQ, Child Health Questionnaire; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PhS, physical summary; PsS, psychosocial summary; RF, rheumatoid factor.

Table 2 Articular parameters of the study patients at baseline; patients are divided into responders and nor responders based on the American College of Rheumatology pediatric (ACR-ped) 30 and 70 criteria

Characteristics	ACR-ped 30 responders (430 (76.4%))	ACR-ped 30 non-responders (133 (23.6%))	ACR-ped 70 responders (225 (40%))	ACR-ped 70 non-responders (338 (60%))
Articular parameters				
No. of active joints	9 (6–15)	10 (6–19)	8 (6–13)*	10 (6–18)
No. of joints with pain	7 (4–13)	8 (4–15)	7 (4–12)	8 (4–15)
No. of swollen joints	7 (4–13)	7 (4–14)	6 (4–11)*	7 (4–14)
No. of joints with limited range of motion	8 (5–13)	7 (4–14)	7 (5–11)	8 (4–15)
Specific joints involvement†				
Wrist: right and left activity	211 (49.1%)	77 (57.9%)	95 (42.2%)**	193 (57.1%)
Wrist: ≥1 active	283 (65.8%)	95 (71.4%)	138 (61.3%)*	240 (71%)
MCP 1: right and left activity	52 (12.1%)*	27 (20.3%)	19 (8.4%)**	60 (17.8%)
MCP 1: ≥1 active	98 (22.8%)	35 (26.3%)	41 (18.2%)*	92 (27.2%)
MCP 2: ≥1 active	156 (36.3%)	57 (42.9%)	69 (30.7%)*	144 (42.6%)
MCP 3: ≥1 active	141 (32.8%)	46 (34.6%)	60 (26.7%)*	127 (37.6%)
PIP 1: right and left activity	59 (13.7%)**	32 (24.1%)	30 (13.3%)	61 (18%)
PIP 2: right and left activity	111 (25.8%)*	48 (36.1%)	52 (23.1%)*	107 (31.7%)
Knee: ≥1 active	351 (81.6%)*	98 (73.7%)	189 (84%)*	260 (76.9%)

Data are N (%) or median (first to third quartile). The denominator is indicated in the table header. Comparisons of frequencies was by χ^2 test, comparison of quantitative variables was by Mann–Whitney U test.
*p<0.05; **p<0.01; ***p<0.001.
†For joint involvement only statistically significant associations are reported.
MCP, metacarpophalangeal; PIP, proximal interphalangeal.

(ACR-ped 30 or 70 responders versus non-responders) was made by the Student's t test or by the Mann–Whitney U test as appropriate, and the comparison of frequencies by the χ^2 test.

A logistic regression analysis was then performed to evaluate the role of baseline variables with ACR-ped 30 or 70 non-responders to MTX. Statistically significant variable (p value<0.05), in the bivariate analysis, were entered into the model. ORs, 95% CIs and the likelihood ratio test were reported.

The programs Statistica 6 (StatSoft, Tulsa, Oklahoma, USA) and Stata 7 (Stata, College Station, Texas, USA) were used.

RESULTS

Of the 563/595 patients (94.6%) available for this analysis, 405 (71.9%) were women. Their median age (first to third quartiles) at onset was 4.3 (1.9–8.4) years, age at study entry 7.7 (4.3–11.4) and disease duration 1.4 (0.7–3.6). The JIA category was polyarticular RF negative in 306 (54.3%), extended oligoarticular in 176 (31.3%) and systemic with polyarticular course in 81 (14.4%) patients. ANA were detected in 259/537 (48.2%) patients, and a history of chronic uveitis was present in 74/546 (13.6%) of patients. At baseline, patients had a median of 9 active joints (6–16), a doctor evaluation of disease activity of 5.1 (3.7–6.6), ESR of 40 mm/I h (21–62), a parent evaluation of child's overall well-being of 4.4 (2.2–6.3), a CHAQ disability index of 1.25 (0.63–1.75) and a Child Health Questionnaire (CHQ) physical well-being of 40.4 (30.5–46.9).

Bivariate analysis

Tables 1 and 2 show the demographic, laboratory, clinical and articular parameters of the patients at study entry divided into ACR-ped 30 and 70 responders and non-responders.

Among the disease characteristics reported in table 1, poor response to MTX according to ACR-ped 30 or 70 criteria was associated with ANA negativity (p<0.001). In addition, poor response according to ACR-ped 70 criteria was associated with longer median disease duration, lower values of ESR and a higher CHAQ level of disability, while a lower parent's evaluation of child's well-being was associated with poor response only according to ACR-ped 30 criteria.

As shown in table 2, when we considered specific patterns of joint involvement, poor response to MTX according to the ACR-ped 70 criteria was associated with the presence of right and left wrist metacarpophalangeal (MCP) 1 activity (p<0.01), ≥1 wrist, MCP 1-2-3, right and left proximal interphalangeal (PIP)s 2, ≥1 knee (all p<0.05). Similar results were obtained for ACR-ped 30 response.

Table 3 Logistic regression models obtained from the evaluations of the determinants of the non-response to MTX, according to the American College of Rheumatology pediatric (ACR-ped) 30 and 70 definition of improvement

Determinants of non-response	OR (95% CI)	p Value*
ACR-ped 30 non-responders (N=128/537 (23.8%)):		
ANA negative	1.92 (1.26 to 2.92)	0.002
CHAQ-DI >1.14	2.18 (1.40 to 3.84)	0.0004
Parent's evaluation of overall well-being ≤4.69	2.20 (1.41 to 3.42)	0.0004
Area under ROC curve of the model	0.65	
ACR-ped 70 non-responders (N=328/537 (61.1%)):		
Disease duration >1.339 years	1.93 (1.34 to 2.77)	0.0003
ANA negative	1.77 (1.23 to 2.55)	0.002
CHAQ-DI >1.125	1.65 (1.15 to 2.38)	0.006
Wrist: right and left activity	1.55 (1.07 to 2.23)	0.019
Area under ROC curve of the model	0.66	

* Likelihood ratio test.
ANA, anti-nuclear antibody; CHAQ-DI, Childhood Health Assessment Questionnaire Disability Index; MTX, methotrexate; ROC, receiver operating characteristic.

Multivariate analysis

All variables that were significantly associated with ACR-ped 30 or 70 poor response were entered into the multivariate logistic regression analysis (table 3). The baseline determinants for poor MTX response according to the ACR-ped 70 criteria were longer disease duration (>1.3 years; OR=1.93), negative ANA (OR=1.77), CHAQ disability index >1.125 (OR=1.65) and the presence of right and left wrist activity (OR=0.65) (eg, patients with both active wrists responded to a lower extent to MTX). Predictors for poor response according to the ACR-ped 30 criteria were similarly ANA negativity, CHAQ disability and, in addition, the parent's evaluation of overall child well-being.

DISCUSSION

In the present study, we have sought for predictors of poor response to a 6-month MTX course in the context of the PRINTO trial.[2] It has been argued that only an improvement in disease activity measures above an ACR-ped 70 threshold reflects a major clinical response to treatment[29] and predicts a more favourable long-term disease outcome in patients with polyarticular-course JIA.[15]

Although it is commonly believed that drug treatments may be more effective if administered early in the course of rheumatoid arthritis[28] or JIA,[16] little evidence-based data exist to support this view. In our study a longer disease duration (>1.3 years) at baseline was the strongest predictor of poorer therapeutic response, suggesting that precocious introduction of second-line medications, in patients who deserve such treatment, increases the likelihood of response.

Previous reports of factors associated with MTX efficacy have provided conflicting results. Halle and Prieur[17] observed that patients who were ANA positive or with polyarticular onset and course were more sensitive to MTX than those with the systemic subtype. Woo *et al*[3] found that MTX was an effective treatment for extended oligoarticular and systemic JIA in a crossover trial. However, Giannini *et al*[1 30] reported an equal response rate among JIA onset subtypes. We previously found that the extended oligoarticular subtype was the best predictor for short-term clinical response to MTX.[9] In the present study the frequency of ILAR categories of JIA was comparable between responders and non-responders. However, ANA negativity was found to be strongly associated with a poorer response to MTX in multivariate analysis, in keeping with previous observation that ANA-positive patients with JIA represent a homogeneous subtype[18] associated with lower disability in children with ≥5 years of disease duration.[19 20]

The finding that a higher level of disability (CHAQ>1.125) at baseline was associated with a greater likelihood of poorer response to MTX is in line with the common view that patients with greater functional impairment/damage are less likely to respond to drug treatments. Patients with JIA with marked functional impairment have been found to have a greater risk of developing long-term physical disability[21] and poorer Health-Related Quality of Life (HRQOL).[22] These findings suggest that early development of functional impairment represents an indication to the start of a more aggressive treatment with biological agents.

Arthritis in both wrists was the best predictor of MTX poor response, with patients who lacked such involvement being more likely to benefit from MTX treatment. It has been suggested that

patients with JIA with polyarthritis and wrist disease are at high risk of experiencing radiographic progression,[23 24] a more severe course of arthritis,[9 25] a poorer functional outcome[26] or a lesser likelihood of short-term therapeutic response.[18] Altogether, these observations emphasise the importance of considering the presence of wrist disease as a marker of poor prognosis in children with JIA.

Limitations of the current work include that the pattern of joint involvement and the observed response rate in JIA cannot be directly compared to adult rheumatoid arthritis due to known heterogeneity of JIA in <5% of the children with RF positivity.[27] Additionally, baseline predictors for a 6-month course of MTX may be different than predictors for a 12-month course of MTX.

In conclusion, we have found that longer disease duration, ANA negativity, a higher level of disability and presence of wrist activity at baseline were significantly associated with a greater likelihood of ACR-ped 70 non-response to a 6-month course of MTX, suggesting that MTX may be distinctly less effective in this subgroup of patients. The presence of these baseline determinants may help doctors to identify patients who might benefit from an earlier treatment with biological drugs.

Acknowledgements We thank the European Union for their support of the project (contract no. BMH4-983531 CA) and the IRCCS G Gaslini. IV was a recipient of European League Against Rheumatism (EULAR) Scientific Training Bursaries. PGM, FS and OA were recipients of a scholarship from the European Union ALFA programme (contract AML/B7-311/97/0666/II-0246-FI). We also acknowledge all remaining colleagues at centres who enrolled patients in the MTX trial. Australia: Kevin J Murray; Belgium: Rik Joos, Carine Wouters; Brazil: Sheila Oliveira, Claudia Saad Magalhães, Virginia Ferriani; Bulgaria: Dimitrina Mihaylova; Czech Republic: Pavla Dolezalova; Finland: Pekka Lahdenne; Germany: Kirsten Minden; Israel: Riva Brik; Italy: Valeria Gerloni, Maria Alessio, Fabrizia Corona, Fernanda Falcini, Francesco Zulian, Maria Giannina Alpigiani, Elisabetta Cortis, Loredana Lepore, Roberta Galasso; Mexico: Ruben Burgos-Vargas; The Netherlands: Nico Wulffraat, Rebecca ten Cate, Renée van Soesberger; Norway: Line Asplin, Berit Flato, Marite Rygg; Slovakia: Richard Vesely; Spain: Julia Garcia-Consuegra, Rosa Merino, Immaculada Calvo; Sweden: Boel Andersson-Gare; Switzerland: Rotraud Saurenmann, Marie-Joseph Sauvain; Turkey: Aysin Bakkaloglu, Huri Ozdogan; UK: Eileen Baildam, Joyce Davidson, Helen Foster, Jo Walsh, Ann Hall, Helen Venning, Pat Woo; USA: Phil Hashkes, Yukiko Kimura.

Competing interests GC is currently a full-time employee of Pfizer.

Ethics approval This study was conducted with the approval of the ethics committees of all participating institutions.

Provenance and peer review Not commissioned; externally peer reviewed.

Patient consent Not obtained.

Authors affiliation [1]IRCCS G Gaslini, Pediatria II, Reumatologia, PRINTO, Genova, Italy
[2]IRCCS G Gaslini, Servizio di Epidemiologia e Biostatistica, Genova, Italy
[3]IRCCS G Gaslini, Pediatria II, Reumatologia and Dipartimento di Pediatria, Università degli Studi, Genova, Italy
[4]Hospital Universitário Clementino Fraga Filho – UFRJ, Reumatologia, Rio De Janeiro, Brasil
[5]Instituto Da Criança – Hospital Das Clinicas, Sao Paulo, Brasil
[6]Deutsches Zentrum für Kinder- und Jugendrheumatologie, Garmisch-Partenkirchen, Germany
[7]Centre Multisite Romand de Rhumatologie Pediatrique/Centre Hospitalier Universitaire Vaudois (CHUV), Hôpitaux Universitaires (HUG), Genève, Lausanne, Switzerland
[8]Hacettepe University Department of Pediatrics, Ankara, Turkey
[9]Landeskrankenhaus Bregenz, Bregenz, Austria
[10]Department of Rheumatology, Hospital for Rheumatic Diseases, Hanyang University, Seoul, South Korea
[11]Hospital Universitário Pedro Ernesto, Núcleo de Estudos da Saúde do Adolescente, Rio de Janeiro, Brasil
[12]Hamburger Zentrum für Kinder- und Jugendrheumatologie, Hamburg, Germany
[13]Professor Hess-Kinderklinik, Bremen, Germany
[14]Hospital Ramon y Cajal, Madrid, Spain
[15]Karolinska University Hospital, Stockholm, Sweden
[16]Medizinische Hochschule Hannover, Hannover, Germany
[17]Haemek Hospital, Afula, Israel
[18]Emma Childrens Hospital AMC and Department of Rheumatology Jan van Breemen Instituut, Amsterdam, The Netherlands
[19]North Bristol NHS Trust, Bristol, UK
[20]New York, NY, USA

REFERENCES

1. **Giannini EH**, Brewer EJ, Kuzmina N, *et al.* Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. *N Engl J Med* 1992;**326**:1043–9.
2. **Ruperto N**, Murray KJ, Gerloni V, *et al.* A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 2004;**50**:2191–201.
3. **Woo P**, Southwood TR, Prieur AM, *et al.* Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. *Arthritis Rheum* 2000;**43**:1849–57.
4. **Lovell DJ**, Giannini EH, Reiff A, *et al.* Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;**342**:763–9.
5. **Ruperto N**, Lovell DJ, Cuttica R, *et al.* A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2007;**56**:3096–106.
6. **Ruperto N**, Lovell DJ, Quartier P, *et al.* Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008;**372**:383–91.
7. **Lovell DJ**, Ruperto N, Goodman S, *et al.* Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008;**359**:810–20.
8. **Ravelli A**, Martini A. Methotrexate in juvenile idiopathic arthritis: answers and questions. *J Rheumatol* 2000;**27**:1830–3.
9. **Ravelli A**, Viola S, Migliavacca D, *et al.* The extended oligoarticular subtype is the best predictor of methotrexate efficacy in juvenile idiopathic arthritis. *J Pediatr* 1999;**135**:316–20.
10. **Céspedes-Cruz A**, Gutiérrez-Suárez R, Pistorio A, *et al.* Methotrexate improves the health-related quality of life of children with juvenile idiopathic arthritis. *Ann Rheum Dis* 2008;**67**:309–14.
11. **Ruperto N**, Martini A. International research networks in pediatric rheumatology: the PRINTO perspective. *Curr Opin Rheumatol* 2004;**16**:566–70.
12. **Petty RE**, Southwood TR, Baum J, *et al.* Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol* 1998;**25**:1991–4.
13. **Petty RE**, Southwood TR, Manners P, *et al.* International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;**31**:390–2.
14. **Giannini EH**, Ruperto N, Ravelli A, *et al.* Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;**40**:1202–9.
15. **Bartoli M**, Tarò M, Magni-Manzoni S, *et al.* The magnitude of early response to methotrexate therapy predicts long-term outcome of patients with juvenile idiopathic arthritis. *Ann Rheum Dis* 2008;**67**:370–4.
16. **Ravelli A**, Ramenghi B, Di Fuccia G, *et al.* Factors associated with response to methotrexate in systemic-onset juvenile chronic arthritis. *Acta Paediatr* 1994;**83**:428–32.
17. **Halle F**, Prieur AM. Evaluation of methotrexate in the treatment of juvenile chronic arthritis according to the subtype. *Clin Exp Rheumatol* 1991;**9**:297–302.
18. **Felici E**, Novarini C, Magni-Manzoni S, *et al.* Course of joint disease in patients with antinuclear antibody-positive juvenile idiopathic arthritis. *J Rheumatol* 2005;**32**:1805–10.
19. **Ruperto N**, Levinson JE, Ravelli A, *et al.* Long-term health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. I. Outcome status. *J Rheumatol* 1997;**24**:945–51.
20. **Ruperto N**, Ravelli A, Levinson JE, *et al.* Long-term health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. II. Early predictors of outcome. *J Rheumatol* 1997;**24**:952–8.
21. **Magni-Manzoni S**, Pistorio A, Labò E, *et al.* A longitudinal analysis of physical functional disability over the course of juvenile idiopathic arthritis. *Ann Rheum Dis* 2008;**67**:1159–64.
22. **Oliveira S**, Ravelli A, Pistorio A, *et al.* Proxy-reported health-related quality of life of patients with juvenile idiopathic arthritis: the Pediatric Rheumatology International Trials Organization multinational quality of life cohort study. *Arthritis Rheum* 2007;**57**:35–43.
23. **Magni-Manzoni S**, Rossi F, Pistorio A, *et al.* Prognostic factors for radiographic progression, radiographic damage, and disability in juvenile idiopathic arthritis. *Arthritis Rheum* 2003;**48**:3509–17.
24. **Cassone R**, Falcone A, Rossi F, *et al.* Unilateral destructive wrist synovitis in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2004;**22**:637–42.
25. **Al-Matar MJ**, Petty RE, Tucker LB, *et al.* The early pattern of joint involvement predicts disease progression in children with oligoarticular (pauciarticular) juvenile rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:2708–15.

26. **Oen K**. Long-term outcomes and predictors of outcomes for patients with juvenile idiopathic arthritis. *Best Pract Res Clin Rheumatol* 2002;**16**:347–60.
27. **Ravelli A**, Martini A. Juvenile idiopathic arthritis. *Lancet* 2007;**369**:767–78.
28. **Anderson JJ**, Wells G, Verhoeven AC, *et al.* Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. *Arthritis Rheum* 2000;**43**:22–9.
29. **Pincus T**, Sokka T, Kavanaugh A. Relative versus absolute goals of therapies for RA: ACR 20 or ACR 50 responses versus target values for "near remission" of DAS or single measures. *Clin Exp Rheumatol* 2004;**22**(5 Suppl 35):S50–6.
30. **Reiff A**, Shaham B, Wood BP, *et al.* High dose methotrexate in the treatment of refractory juvenile rheumatoid arthritis. *Clin Exp Rheumatol* 1995;**13**: 113–18.

Predictors of poor response to methotrexate in polyarticular-course juvenile idiopathic arthritis: analysis of the PRINTO methotrexate trial

Iris Vilca, Pablo Garcia Munitis, Angela Pistorio, et al.

Ann Rheum Dis published online June 4, 2010
doi: 10.1136/ard.2009.120840